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(54) Delayed, Sustained-release pharmaceutical preparation

Arzneimittelzubereitung mit verspätet einsetzender kontinuierlicher Freisetzung

Préparation pharmaceutique à libération retardée et continue

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(73) Proprietor:
KINAFORM TECHNOLOGY INC.
Dayton, Ohio 45459 (US)

(72) Inventor: **Massmann, Brent D.**
St. Louis, Missouri 63146 (US)

(74) Representative:
Homer, Martin Grenville et al
Cruikshank & Fairweather
19 Royal Exchange Square
Glasgow G1 3AE Scotland (GB)

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• **JOURNAL OF CONTROLLED RELEASE vol. 14,**
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203 - 213 XP165641 A.G. OZTURK ET AL.
'mechanism of release from pellets coated with
an ethylcellulose-based film'

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Description

The present invention relates to multi-unit, delayed, sustained-release pharmaceutical preparations, and more particularly, to microparticles formed of a water-soluble core drug coated with a single, hydratable diffusion barrier which allows a prolonged delayed and sustained release drug delivery.

As is well known, the maximum time of effectiveness in many pharmaceutical preparations, particularly those containing a drug such as aspirin, acetaminophen, indomethacin, propranolol hydrochloride, dextromethorphan, etc. is only a few hours because of biological modification and/or elimination of the medication in the body. Consequently, repeated doses must be taken at frequent intervals to obtain long term therapeutic levels of drug. Furthermore, these drugs usually dissolve readily in the digestive juices and the total dosage is immediately fed into the blood stream. After high initial peak concentrations, the level of drug in the blood stream constantly decreases because of the biological elimination, so there is little or no therapeutic effect at the end of the period between doses. As a result, the therapeutic effect fluctuates between doses corresponding to the peaks and valleys in the level of drug in the blood.

Many attempts have been made to develop timed-release pharmaceutical preparations which provide a more constant level of the drug in the blood over several hours.

One common approach is to microencapsulate aspirin, for example, with a capsule wall material which provides a slower dissolution rate than free aspirin. The early work in that regard is represented by U.S. Pat. Nos. 3,155,590; 3,341,416; 3,488,418; and 3,531,418. Those patents, among others, disclose dispersing particles of aspirin in a hot cyclohexane solution containing ethyl cellulose and then introducing a phase-separation inducing agent, such as butyl rubber or polyethylene. Upon cooling, the aspirin particles become coated with ethyl cellulose. The coated particles are then admixed with tableting excipients and formed into dosage-sized tablets. When ingested, the tablets disintegrate rapidly and the individual particles of encapsulated aspirin are dispersed in the stomach. The gastric juices slowly diffuse through the capsule walls, dissolve the aspirin, and the dissolved aspirin slowly diffuses or leaches out through the capsule walls into the body. Although the resultant blood level content is sustained to a measurable extent, the aspirin is diffused into the body rapidly enough so there is an initially high blood level content which decreases quite rapidly within a few hours.

As a result, efforts have been made to adjust the rate of dissolution and, thus, control the timing of sustained drug release. See, for example, Peters, U.S. Patent No. 3,492,397 where the dissolution rate is said to be controlled by adjusting the wax/ethyl cellulose ratio of the applied spray coating, and Mehta, U.S. Patent No.

4,752,470 where the controlled release characteristics for indomethacin are varied depending on the ratio of ethyl cellulose to hydroxypropyl cellulose in the coating. See also U.S. Patents No. 4,205,060 and 3,488,418 where it is indicated that the rate of dissolution of various drugs can be controlled by varying the thickness of the coating applied to those drugs.

Another method for providing an encapsulated pharmaceutical composition is discussed in published European patent Application No. 77,956, published May 4, 1983. EPO Publication No. 77,956 discloses the use of microcapsules containing a coated core material such as pharmaceutical compounds and foodstuffs. The coating is applied by dispersing the core material into a solution containing ethyl cellulose as the wall-forming material. A phase separation of the ethyl cellulose from the dispersion of core material is carried out by cooling the dispersion. During this cooling, an enteric polymer material is incorporated into the ethyl cellulose coating walls by adding the enteric polymer material with stirring while the ethyl cellulose is still in the "gel" state. The enteric polymer material thus added penetrates and is dispersed into the coating walls. When the microcapsules are administered, the release of the active compound does not generally occur in the stomach. However, the enteric polymer material is easily dissolved in the intestinal tract, thereby making the microcapsules porous. The porosity of the microcapsules promotes the rapid release of the active compound in the intestinal tract.

A similar approach is found in Japanese Patent Publication No. 12614/81, published March 23, 1981. Japanese Publication No. 12614/81 discloses an enteric protective coating composition which will not readily dissolve in acidic gastric juices, but rapidly (within minutes) dissolves at the pH found in the intestines. The enteric coating is an aqueous dispersion of, for example, hydroxy propyl methyl cellulose phthalate, a gelling agent such as diacetin, and hydroxy propyl methyl cellulose. See, also, Japanese Patent Publication No. 11687/81, published March 16, 1981, which uses hydroxy propyl methyl cellulose phthalate as an enteric coating.

The systems described in the EPO and Japanese publications are essentially "delayed" release mechanisms. There is a delay of medicament release in the stomach, but once the coated medicament reaches the intestines, the release of medication is rapid. There is no sustained release of medication in the intestines.

Still other systems for sustained-release pharmaceutical preparations are known. For example, Fukui et al, U.S. Patent No. 4,772,475, relate to a controlled-release pharmaceutical formulation comprising a granular core mixed with water-insoluble polymers such as acrylic acid polymers and copolymers, and cellulose derivatives which allows gradual release of the drug in the gastrointestinal tract.

Mughal et al, U.S. Patent No. 4,524,060, relate to a

sustained-release pharmaceutical composition comprising a mixture of micronised indoramin, a water-channeling agent such as microcrystalline cellulose, and a wetting agent comprising anionic surfactants. The mixture is coated with an enteric coating such as hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate and acrylic resins, or a sustained-release coating such as natural waxes or mixtures of polymers, such as ethyl cellulose, which is permeable to gastro-intestinal juices.

Barry et al, U.S. Patent No. 4,900,558 disclose a pharmaceutical formulation providing sustained release over a 12-hour period comprising a drug core containing ibuprofen and microcrystalline cellulose, and a coating covering the core comprising a water-insoluble but water-swelling acrylic polymer and a water-soluble hydroxylated cellulose derivative.

In addition, Published EPO application 212745 discloses sustained-release drug particles containing an ibuprofen drug core, an inner coating of an enteric material such as acrylic polymers and copolymers, and an outer coating such as methacrylic acid polymers and copolymers which are insoluble at any pH and act as a diffusion barrier for the drug.

While the above-mentioned references provide a more constant rate of drug release, in some instances, it is desirable to mix the delayed sustained-release preparation with an immediate release drug to obtain a biphasic drug release profile. For example, Radebaugh et al, U.S. Patent No. 4,968,509, disclose a sustained-release acetaminophen formulation formed by mixing acetaminophen with hydroxyethyl cellulose and a wicking agent such as microcrystalline cellulose, and then adding a povidone granulating agent. The sustained-release formulation may be part of a multi-layered tablet containing an immediate-release layer of acetaminophen to quickly elevate and then maintain the blood levels of acetaminophen.

Reference is also made to Eichel, U.S. Patent No. 5,026,559, which discloses a delayed and sustained-release pharmaceutical preparation comprising a multi-walled coated drug having an inner wall microencapsular enteric coating, such as polymethacrylic acid/acrylic acid copolymer or cellulose acetate phthalate, a solid acid either incorporated in the enteric layer or layered over the enteric layer, and an outer wall microencapsulated control coating such as polymethacrylic acid ester copolymer or ethyl cellulose. The solid acid delays drug release by maintaining the enteric polymer in an impermeable state until the acid diffuses out of the drug or is neutralized. The multi-walled coated drug is admixed with an uncoated drug having immediate therapeutic properties upon dissolution in the stomach.

However, many of the multi-walled preparations described above do not provide prolonged delayed release of the drug prior to initiation of sustained release, which is important when biphasic release profiles are desired.

EP-A-O-436 370 relates to a controlled release pharmaceutical preparation which comprises (a) a core containing a pharmaceutically active substance and an organic acid, and b) an outer coating film on the surface of the preparation, said film being formed by aqueous coating of a water-insoluble and slightly water-permeable acrylic polymer containing a trimethylammonium-ethyl group. EP-A-O-436 370 teaches that the coating can be a combination of Eudragit RL and Eudragit RS, such a combination is also taught by Lehman, K in Acta Pharm. Technol. 32(3) 146-152 (1986).

Ozturk et al (J. Controlled Release 14 (1990) 203-213) discloses to drug release from pellets coated with an ethyl cellulose-based pseudolatex for use as a sustained release coating for pharmaceuticals. Similarly EP-A-O- 284-039 relates to sustained slow-release pharmaceutical compositions.

EP-A-O-322-277 shows the combination of a film forming polymer (ethyl cellulose) and an additive (Eudragit RS) in ratios of 6:4 to 4:6

Accordingly, the need exists for a delayed, sustained-release pharmaceutical preparation which provides a longer delay of drug dissolution which would provide greater flexibility in designing sustained-release profiles for a wide variety of drugs, provides constant blood concentration levels, is simply and economically produced, and has the advantages of a multi-units formulation.

The present invention provides a delayed, sustained-release pharmaceutical preparation comprising:

(a) a core containing a water-soluble drug having a solubility of greater than 10 grams per liter in intestinal fluid,

(b) a hydratable diffusion barrier surrounding said core and having a thickness of at least 20 microns, said barrier comprising

a film-forming polymer which is insoluble under both stomach and intestinal conditions, said film-forming polymer being an acrylic resin or ethyl cellulose, and an additive to control the hydration rate and permeability of said hydratable diffusion barrier, said additive being selected from fully esterified acrylic resins containing quaternary amine side chains, sodium lauryl sulfate, magnesium stearate, citric acid, simethicone, and mixtures thereof; whereby said hydratable diffusion barrier substantially delays release of therapeutic levels of said drug for 2-10 hours after ingestion, and thereafter provides for sustained-release of therapeutic levels of said drug.

Thus, the diffusion barrier of the present invention initially prevents drug release, and is then slowly hydrated to become permeable to dissolved drug and provide a sustained release of the drug.

The length of time for the delay is controlled by the rate of hydration and the thickness of the diffusion barrier. The drug release rate subsequent to the delay is determined by the thickness and permeability of the hydrated diffusion barrier. The drug release rate subsequent to the delay is determined by the thickness and permeability of the hydrated diffusion barrier. Thus, it is possible to regulate the rate of hydration and permeability of the diffusion barrier so that the desired delayed, sustained-release drug profiles can be achieved.

The hydratable diffusion barrier preferably comprises film-forming polymers which are insoluble under intestinal conditions and additives which control the rate of hydration and permeability of the diffusion barrier. The diffusion barrier is preferably at least about 20 microns thick. The preferred insoluble film-forming polymers are aqueous dispersions of fully esterified acrylic resins such as Eudragit NE30D available from Rohm Pharma GmbH of Weiterstadt, Germany, aqueous dispersions of ethyl cellulose such as Aquacoat ethylcellulose emulsion, available from FMC Corp. of Chicago, Illinois or Surelease, available from Colorcon of West Point, Pennsylvania. Polymers dissolved in organic solvents may also be used.

The additives which control the rate of hydration and permeability of the diffusion barrier are preferably selected from the group consisting of fully esterified acrylic resins containing quaternary amine side chains, anionic surfactants, lubricants, plasticizers, inert water soluble materials, and mixtures thereof. In a preferred embodiment, these additives comprise fully esterified acrylic resins containing quaternary amine side chains such as Eudragit RS30D and RL30D available from Rohm Pharma, sodium lauryl sulfate, magnesium stearate, citric acid, simethicone, and mixtures thereof. The use of acrylic resins such as Eudragit RS30D and RL30D increases the permeability of the diffusion barrier without significantly affecting the hydration rate. This increased permeability allows thicker diffusion barriers to be used to provide longer time delays while still releasing drug at desirable rates.

Magnesium stearate decreases the hydration rate, increases the hydrated permeability of the diffusion barrier, and also prevents the drug beads from agglomerating during processing. Preferably, the magnesium stearate is used in an amount of approximately 0 to 50% of the weight of the film-forming polymers.

Anionic surfactants are preferably used in an amount of from approximately 0 to 2% of the film-forming polymer weight, and function to increase both the permeability and hydration rate of the diffusion barrier. Inert, water-soluble materials are preferably used in amounts of approximately 0 to 20% of the film-forming polymer weight, and also increase both the permeability and hydration rate of the diffusion barrier.

Suitable plasticizers include either hydrophilic or hydrophobic plasticizers. Hydrophilic plasticizers increase both the permeability and hydration rate of the

diffusion barrier, while hydrophobic plasticizers decrease both the permeability and hydration rate of the diffusion barrier. The plasticizers are preferably used at amounts from approximately 0-30% of the film-forming polymer weight.

The core drug is preferably a water soluble drug having a solubility of greater than approximately 10 grams per liter in intestinal fluid. Preferred drugs are propranolol hydrochloride, guinidine gluconate, diltiazem hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide phosphate, and verapamil hydrochloride. The core drug may be coated on sugar spheres, blended with wax incipients, or otherwise formulated to produce core drug granules. Preferably, the core drug granules are spherical microparticles having a size range from about 500 to 1500 microns.

The hydratable diffusion barrier is formed by combining the film-forming polymer and additive which controls the rate of hydration and permeability of the diffusion barrier, and then coating the mixture onto core drug granules by a spray coating process, resulting in a hydratable diffusion barrier having a thickness of at least 20 microns.

The multi-unit microparticles may also be admixed or concentrically coated with other fractions of an immediate-release drug to provide for both immediate and delayed sustained release of the drug.

In another embodiment of the invention, the multi-unit microparticles may also be admixed with conventional sustained-release microparticles or be concentrically coated by a drug layer overcoated by a conventional sustained-release coating. This combination provides an immediate yet sustained release of drug along with the hydratable diffusion barrier's delayed sustained release.

In yet another embodiment of the invention, a conventional diffusion barrier selected from the group consisting of methacrylic acid ester copolymer and ethyl cellulose is concentrically coated beneath the hydratable diffusion barrier. This combination of a conventional diffusion barrier with a hydratable diffusion barrier provides for slower release of the drug.

Accordingly, it is an object of the present invention to provide a delayed, sustained-release pharmaceutical preparation having a single, hydratable diffusion barrier coated on a core drug which allows prolonged delayed and sustained-release drug delivery.

These, and other objects and advantages of the present invention will become apparent from the following detailed description, and the appended claims.

The preferred delayed, sustained-release pharmaceutical preparation of the present invention is a water soluble core drug surrounded by a hydratable diffusion barrier comprising an insoluble film-forming polymer such as Eudragit NE30D (Rohm Pharma) and an additive which controls the rate of hydration and permeability of the diffusion barrier, together in microparticle form.

The core drug is preferably a soluble orally administered drug which provides sustained release over periods of 4 to 24 hours. The solubility of the drug in the intestines should be greater than 10 grams per liter as drugs with lower solubility will not dissolve and diffuse through the hydrated diffusion barrier at adequate rates. Examples of suitable drugs include propranolol hydrochloride, guinidine gluconate, diltiazem hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide phosphate, and verapamil hydrochloride.

The hydratable diffusion barrier is formed by combining the film-forming polymer and additives which control the rate of hydration and permeability of the diffusion barrier, and then spray coating the core drug. As mentioned previously, the film-forming polymer may comprise Eudragit NE30D while the additives may include Eudragit RS30D and RL30D. The Eudragit RS30D and RL30D are aqueous dispersions of film-forming polymers, and may be combined with the insoluble film-forming polymer in any proportion to achieve the desired permeability. Preferably, when mixing the film-forming polymer such as Eudragit NE30D with additives such as Eudragit RS30D and RL30D, an anionic surfactant is added to the NE30D in an amount of about 1% to prevent the dispersions from becoming unstable. Thus, in the most preferred embodiment, the additive is a mixture of materials used to achieve the desired hydration and permeability of the diffusion barrier.

In one embodiment, the additive comprises from about 3 to 50% of a fully esterified acrylic resin suspension containing quaternary amine side chains such as Eudragit RS30D or RL30D, from about 0 to 1% sodium lauryl sulfate, from about 10 to 20% magnesium stearate, and from about 40 to 87% water.

In another embodiment, the additive comprises from about 5 to 20% magnesium stearate, from about 75 to 95% water, and from about 0 to 5% citric acid.

In yet another embodiment, the additive comprises from about 5 to 20% magnesium stearate, from about 80 to 95% water, and 0 to 1% simethicone emulsion.

The preferred process for applying the hydratable diffusion barrier to the core drug is a fluid bed spray coating process such as the Wurster process or the tangential spray rotor process. Other spray coating processes such as pan coating or the immersion tube process may be used. The additive comprises 5-40% (solids basis) of the combined aqueous dispersion. The drug beads are coated with the dispersion and tray dried at 35°C to 60°C for 8 hours to 5 days (120 hours).

The diffusion barrier should be at least 20 microns thick to obtain delays of 2 hours or longer and is preferably 30 to 200 microns thick. The upper limit of the diffusion barrier thickness is determined by the potency requirements for the formulation. The permeability of the hydrated diffusion barrier should be designed to provide the desired release rate of the drug after the delay

has elapsed.

The resulting multi-unit microparticles may be admixed or concentrically coated with other fractions of an immediate-release drug. The admixture or concentrically coated microparticles may be placed in either capsules or tablets along with other usual ingredients such as binders, fillers, lubricants, etc. In these forms free drug is released immediately in the stomach, while the drug having the hydratable diffusion barrier does not release drug until after a time delay determined by the thickness and permeability of the hydratable diffusion barrier. The drug is then released slowly and steadily from the hydratable diffusion barrier coated portion of the formulation. The admixture or concentrically coated microparticles, thus, provide for both immediate and delayed sustained release of the drug.

The microparticles may also be admixed with conventional sustained-release microparticles or concentrically coated by drug followed by a conventional diffusion barrier. The sustained-release portion of the drug is released slowly from the time of administration. This release is followed by the delayed, sustained release through the hydratable diffusion barrier after permeation by water. Conventional diffusion barrier materials include Eudragit NE30D acrylic resin (Rohm Pharma) or Aquacoat ethylcellulose emulsion (FMC).

A conventional diffusion barrier coated under the hydratable diffusion barrier may be used to modify the delayed, sustained release of drug. Conventional diffusion barrier materials may be a neutral coat such as Eudragit NE30D or Aquacoat, or any other conventional diffusion barrier which produces immediate but sustained release.

In order that the invention may be more readily understood, reference is made to the following examples, which are intended to illustrate the invention, but are not to be taken as limiting the scope thereof.

Example I

60% active propranolol hydrochloride beads were prepared by coating a solution of propranolol hydrochloride in water onto 25-30 mesh sugar spheres. A diffusion barrier coating formulation was prepared by combining 67.6 parts by weight Eudragit NE30D from Rohm Pharma with 0.1 part by weight sodium lauryl sulfate. 3.6 parts by weight magnesium stearate was dispersed into 25.1 parts by weight water and added to the Eudragit NE30D and sodium lauryl sulfate. 3.6 parts by weight Eudragit RS30D from Rohm Pharma was then added with stirring. In a fluidized bed with a Wurster insert 425 grams of the 60% propranolol beads were coated with the coating formulation using a spray rate of 7 grams per minute and an inlet temperature of 30°C. Samples were taken after spraying 425 grams (20% coat), 507 grams (25% coat) and 729 grams (30% coat). The coated beads were tray dried at 40°C for 18 hours. The dissolutions were performed by the U.S.P.

basket dissolution method at 100 rpm in 1 liter of 0.05 M pH 6.8 phosphate buffer. The results of a dissolution study are set forth in Table 1 below.

Table I

Propranolol Hydrochloride Dissolution			
Time (hrs)	Percent Dissolved		
	20% coat	25% coat	30% coat
2	1%	0%	0%
4	3%	2%	0%
5	7%	2%	0%
6	16%	3%	0%
7	32%	6%	0%
8	53%	13%	1%
10	83%	36%	3%
12	93%	67%	13%
13	98%	79%	21%

Example II

50% active diltiazem hydrochloride beads were prepared by coating a solution of 27.3 parts by weight diltiazem, 0.5 parts hydroxy propyl methylcellulose, 0.8 parts microcrystalline cellulose, and 1.4 parts magnesium stearate in 70 parts water. 425 grams of the 50% active diltiazem beads were coated with the coating formulation described in Example 1 by the Wurster process. Samples were taken after spraying 189 grams (10% coat), 277 grams (14% coat) and 373 grams (18% coat). The coated beads were tray dried at 40°C for 18 hours. The dissolutions were performed as in Example I and the results are set forth in Table II below.

Table II

Diltiazem Hydrochloride Dissolution			
Time (hrs)	Percent Dissolved		
	10% coat	14% coat	18% coat
2	3%	3%	2%
4	16%	4%	2%
6	44%	15%	3%
8	73%	38%	11%
10	85%	59%	28%
14	96%	82%	59%
18	100%	93%	77%

Example III

53% active diltiazem HCl beads were prepared by coating 25-30 mesh sugar spheres with a solution of 27.8 parts diltiazem HCl in 70 parts water containing 2.2 parts microcrystalline cellulose. A coating formulation was prepared by dispersing 10.8 parts magnesium stearate in 17.2 parts water containing 0.2 parts citric acid and adding to 64.6 parts Eudragit NE30D from Rohm Pharma and 7.2 parts Aquacoat from FMC. 318 grams of this coating formulation was coated onto 450 grams of the 53% active diltiazem HCl beads using the Wurster process spraying at 5.5 grams per minute with an inlet temperature of 30°C. The coated beads were dried 18 hours at 40°C. The dissolution was performed as in Example I and the results are set forth in Table III below.

Table III

Diltiazem Hydrochloride Dissolution	
Time (hrs)	Percent Dissolved 15% Coat
2	2%
4	5%
6	34%
8	59%
10	73%
14	81%
18	89%

Example IV

65% active disopyramide phosphate beads were prepared by coating a solution of 50 parts disopyramide phosphate, 2.5 parts Povidone K30, a binder available from GAF of Texas City, Texas, 0.2 parts talc, and 47.3 parts water onto 25-30 mesh sugar spheres using the Wurster process. A coating formulation was prepared by dispersing 3.3 parts magnesium stearate in 31 parts water containing 0.1 part simethicone emulsion USP and adding it to 65.6 parts Eudragit NE30D from Rohm Pharma. The coating formulation was applied to 3500 grams of the 65% active disopyramide phosphate beads by the Wurster process using a spray rate of 40 grams per minute and an inlet air temperature of 40°C. Samples were taken after spraying 3454 grams (18.5% coat), 4292 grams (22% coat), and 5918 grams (28% coat). Dissolutions were performed as in Example I and are set forth in Table IV-A below.

Table IV-A

Disopyramide Phosphate Dissolution			
Time (hrs)	Percent Dissolved		
	18.5% coat	22% coat	28% coat
1	1%	0%	0%
2	2%	0%	0%
3	5%	0%	0%
5	13%	4%	2%
8	29%	14%	8%
12	65%	50%	29%
16	87%	81%	49%
20	100%	96%	68%
24	100%	99%	85%

The disopyramide phosphate beads with the 28% coat were tested in healthy human subjects to determine the concentration of drug in plasma versus time after dosing. A single dose containing 300 mg of disopyramide was administered to four subjects. Blood samples were taken over a 24 hour period and the plasma concentration of disopyramide was determined. The results presented in Table IV-B show that the delayed then sustained release profile occurs in human subjects as well as during in vitro dissolution testing. Drug is not detected in the plasma until 4 hours after dosing. The drug plasma concentration then increases to a plateau which is maintained from 18 to 24 hours.

Table IV-B

Disopyramide Phosphate Biostudy 300 mg dose, 28% coated beads	
Time After dose (hrs)	Plasma Disopyramide mg/L
2	0
4	0.09
8	0.39
12	0.65
16	1.07
18	1.16
22	1.16
24	1.18

Example V

This example illustrates the concentric coating of a fast release component onto the delayed sustained-release disopyramide phosphate of Example IV. 500 grams of the 28% coated beads from Example IV were coated with 130 grams of a coating formula composed of 47.5 parts disopyramide phosphate, 2.5 parts talc, 2.5 parts Povidone K30 from GAF, and 47.5 parts water using the Wurster process with a spray rate of 4.5 grams per minute and an inlet temperature of 50°C. These beads were then coated with 118 grams of a coating formula composed of 57 parts Eudragit NE30D from Rohm Pharma, 3 parts magnesium stearate, and 40 parts water. The dissolution procedure described in Example I resulted in the release rate profile shown in Table V. The concentrically coated fast release component provides drug release for the first 4 hours then release from the second slow release component initiates at about 7 hours.

Table V

Disopyramide Biphasic Release	
Time (hrs)	Percent Dissolved Disopyramide mg/L
1	5%
2	10%
4	18%
8	27%
12	42%
16	61%
20	75%
24	87%

While certain representative embodiments and details have been shown for purposes of illustrating the invention, it will be apparent to those skilled in the art that various changes in the methods and apparatus disclosed herein may be made without departing from the scope of the invention, which is defined in the appended claims.

Claims

1. A delayed, sustained-release pharmaceutical preparation comprising:

- (a) a core containing a water-soluble drug having a solubility of greater than 10 grams per liter in intestinal fluid,
- (b) a hydratable diffusion barrier surrounding said core and having a thickness of at least 20

microns, said barrier comprising

a film-forming polymer which is insoluble under both stomach and intestinal conditions, said film-forming polymer being an acrylic resin or ethyl cellulose, and an additive to control the hydration rate and permeability of said hydratable diffusion barrier, said additive being selected from fully esterified acrylic resins containing quaternary amine side chains, sodium lauryl sulfate, magnesium stearate, citric acid, simethicone, and mixtures thereof; whereby said hydratable diffusion barrier substantially delays release of therapeutic levels of said drug for 2-10 hours after ingestion, and thereafter provides for sustained-release of therapeutic levels of said drug.

2. The delayed, sustained-release pharmaceutical preparation of claim 1 wherein said water-soluble drug is selected from propranolol hydrochloride, guinidine gluconate, diltiazem hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide phosphate, and verapamil hydrochloride.
3. The delayed, sustained-release pharmaceutical preparation of claim 1 wherein said additive prior to being added to the film-forming polymer and being coated onto said core drug comprises from 3 to 50% of a fully esterified acrylic resin suspension containing quaternary amine side chains, from 0 to 1% sodium lauryl sulfate, from 10 to 20% magnesium stearate, and from 40 to 87% water.
4. The delayed, sustained-release pharmaceutical preparation of claim 1 wherein said additive prior to being added to the film-forming polymer and being coated onto said core drug comprises from 5 to 20% magnesium stearate, from 75 to 95% water, and from 0 to 5% citric acid.
5. The delayed, sustained-release pharmaceutical preparation of claim 1 wherein said additive prior to being added to the film-forming polymer and being coated onto said core drug comprises from 5 to 20% magnesium stearate, from 80 to 95% water, and 0 to 1% simethicone emulsion.
6. The delayed, sustained-release pharmaceutical preparation of claim 1 wherein said additive comprises from 5 to 40% (solids basis) of the mixture of film-forming polymer and additive prior to being coated onto said core drug.
7. The delayed, sustained-release pharmaceutical

preparation of claim 1 wherein the thickness of said hydratable diffusion barrier is 30 to 200 microns.

8. The delayed, sustained-release pharmaceutical preparation of claim 7 wherein said core drug is in the form of particles from 500-1500 microns in diameter.
9. The pharmaceutical preparation of claim 1 wherein said delayed, sustained-release component is in the form of multi-units of microparticles and said sustained-release component is in the form of said water-soluble drug concentrically coated on said microparticles and then a diffusion barrier coated thereover.
10. A pharmaceutical preparation comprising a mixture of a delayed, sustained-release component and an immediate release component:

(i) said delayed, sustained-release component comprising

- (a) a core containing a water-soluble drug having a solubility of greater than 10 grams per liter in intestinal fluid,
- (b) a hydratable diffusion barrier surrounding said core and having a thickness of at least 20 microns, said barrier comprising

a film-forming polymer which is insoluble under both stomach and intestinal conditions, said film-forming polymer being an acrylic resin or ethyl cellulose, and an additive to control the hydration rate and permeability of said hydratable diffusion barrier, said additive being selected from fully esterified acrylic resins containing quaternary amine side chains, sodium lauryl sulfate, magnesium stearate, citric acid, simethicone, and mixtures thereof;

whereby said hydratable diffusion barrier substantially delays release of therapeutic levels of said drug for 2-10 hours after ingestion, and thereafter provides for sustained release of therapeutic levels of said drug,

(ii) said immediate release component comprising free drug which is immediately released in the stomach after ingestion.

11. The pharmaceutical preparation of claim 10 wherein said delayed, sustained-release component is in the form of multi-units of microparticles.

12. A pharmaceutical preparation comprising a mixture of a delayed, sustained-release component and a sustained-release component:

(i) said delayed, sustained-release component comprising 5

(a) a core containing a water-soluble drug having a solubility of greater than 10 grams per liter in intestinal fluid, 10
(b) a hydratable diffusion barrier surrounding said core and having a thickness of at least 20 microns, said barrier comprising

a film-forming polymer which is insoluble under both stomach and intestinal conditions, said film-forming polymer being an acrylic resin or ethyl cellulose, 15
and an additive to control the hydration rate and permeability of said hydratable diffusion barrier, said additive being selected from fully esterified acrylic resins containing quaternary amine side chains, sodium lauryl sulfate, magnesium stearate, citric acid, simethicone, and mixtures thereof; 20

whereby said hydratable diffusion barrier substantially delays release of therapeutic levels of said drug for 2-10 hours after ingestion, and thereafter provides for sustained release of therapeutic levels of said drug, 30

(ii) said sustained-release component comprising a core of said water-soluble drug with a diffusion barrier material thereover. 35

Patentansprüche 40

1. Arzneimittelzubereitung mit verzögerter Langzeitabgabe, umfassend:

(a) einen Kern, welcher ein wasserlösliches Arzneimittel mit einer Löslichkeit von größer als 10 Gramm pro Liter in der Darmflüssigkeit enthält, 45
(b) eine hydratisierbare Diffusionsbarriere, die den Kern umgibt und eine Dicke von mindestens 20 Mikrometern aufweist, wobei die Barriere umfaßt 50

ein filmbildendes Polymer, welches sowohl unter Magen- wie auch Darmbedingungen unlöslich ist, wobei das filmbildende Polymer ein Acrylharz oder Ethylcellulose ist, und 55

ein Additiv zum Kontrollieren der Hydratationsgeschwindigkeit und Permeabilität der hydratisierbaren Diffusionsbarriere, wobei das Additiv aus vollständig veresterten Acrylharzen ausgewählt ist, die quaternäre Aminnebenketten, Natriumlaurylsulfat, Magnesiumstearat, Zitronensäure, Simethicon und Mischungen davon enthalten;

wobei die hydratisierbare Diffusionsbarriere im wesentlichen die Abgabe von therapeutischen Spiegeln des Arzneimittels 2-10 Stunden nach der Aufnahme verzögert und anschließend eine Langzeitabgabe von therapeutischen Spiegeln des Arzneimittels liefert.

2. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 1, wobei das wasserlösliche Arzneimittel aus Propranololhydrochlorid, Guinidingluconat, Diltiazemhydrochlorid, Dextromethorphanhydrobromid, Diphenhydraminhydrochlorid, Diisopyramidphosphat und Verapamilhydrochlorid ausgewählt ist.

3. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 1, wobei das Additiv, bevor es zu dem filmbildenden Polymeren hinzugefügt und auf das Kernarzneimittel aufgetragen wird, 3 bis 50% einer Suspension von vollständig verestertem Acrylharz, enthaltend quaternäre Aminnebenketten, 0 bis 1% Natriumlaurylsulfat, 10 bis 20% Magnesiumstearat und 40 bis 87% Wasser enthält.

4. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 1, wobei das Additiv, bevor es zu dem filmbildenden Polymeren hinzugefügt und auf das Kernarzneimittel aufgetragen wird, 5 bis 20% Magnesiumstearat, 75% bis 95% Wasser und 0 bis 5% Zitronensäure umfaßt.

5. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 1, wobei das Additiv, bevor es zu dem filmbildenden Polymeren hinzugefügt und auf das Kernarzneimittel aufgetragen wird, 5 bis 20% Magnesiumstearat, 80 bis 95% Wasser und 0 bis 1% Simethiconemulsion umfaßt.

6. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 1, wobei das Additiv 5 bis 40% (Feststoffbasis) der Mischung aus dem filmbildenden Polymeren und Additiv, bevor es auf das Kernarzneimittel aufgetragen wird, umfaßt.

7. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 1, wobei die Dicke der hydratisierbaren Diffusionsbarriere 30 bis 200 Mikrometer beträgt.

8. Arzneimittelzubereitung mit verzögerter Langzeitabgabe nach Anspruch 7, wobei das Kernarzneimittel in der Form von Teilchen von 500-1500 Mikrometer an Durchmesser vorliegt. 5
9. Arzneimittelzubereitung nach Anspruch 1, wobei die Komponente mit verzögerter Langzeitabgabe in der Form von Multi-Einheiten von Mikroteilchen vorliegt, und die Komponente mit Langzeitabgabe in der Form des wasserlöslichen Arzneimittels ist, welches konzentrisch auf die Mikroteilchen aufgetragen ist, und anschließend ist eine Diffusionsbarriere darüber aufgetragen. 10
10. Pharmazeutische Zubereitung, umfassend eine Mischung aus einer Komponente mit verzögerter Langzeitabgabe und eine unmittelbare Abgabekomponente, wobei 15
- (i) die Komponente mit verzögerter Langzeitabgabe umfaßt: 20
- (a) einen Kern, welcher ein wasserlösliches Arzneimittel enthält, mit einer Löslichkeit von mehr als 10 Gramm pro Liter in der Darmflüssigkeit, 25
- (b) eine hydratisierbare Diffusionsbarriere, die den Kern umgibt und eine Dicke von mindestens 20 Mikrometer hat, wobei die Barriere umfaßt 30
- ein filmbildendes Polymer, welches sowohl unter Magen- wie auch Darmbedingungen unlöslich ist, wobei das filmbildende Polymer ein Acrylharz oder Ethylcellulose ist, und 35
- ein Additiv zum Kontrollieren der Hydratationsgeschwindigkeit und Permeabilität der hydratisierbaren Diffusionsbarriere, wobei das Additiv ausgewählt ist aus vollständig veresterten Acrylharzen, welche quaternäre Aminnebenketten enthalten, Natriumlaurylsulfat, Magnesiumstearat, Zitronensäure, Simethicon und Mischungen davon; 40
- wobei die hydratisierbare Diffusionsbarriere im wesentlichen die Abgabe von therapeutischen Spiegeln des Arzneimittels 2 bis 10 Stunden nach Aufnahme verzögert und anschließend eine Langzeitabgabe von therapeutischen Spiegeln des Arzneimittels liefert, 45
- (ii) wobei die unmittelbare Abgabekomponente das freie Arzneimittel, welches unmittelbar in den Magen nach Aufnahme abgegeben wird, 50
- 55

umfaßt.

11. Pharmazeutische Zubereitung nach Anspruch 10, wobei die Komponente mit verzögerter Langzeitabgabe in der Form von Multi-Einheiten von Mikroteilchen vorliegt.

12. Pharmazeutische Zubereitung, umfassend eine Mischung aus einer Komponente mit verzögerter Langzeitabgabe und eine Komponente mit Langzeitabgabe, wobei

(i) die Komponente mit verzögerter Langzeitabgabe umfaßt:

(a) einen Kern, welcher ein wasserlösliches Arzneimittel mit einer Löslichkeit von größer als 10 Gramm pro Liter in der Darmflüssigkeit enthält,

(b) eine hydratisierbare Diffusionsbarriere, die den Kern umgibt und eine Dicke von mindestens 20 Mikrometern aufweist, wobei die Barriere umfaßt

ein filmbildendes Polymer, welches sowohl unter Magen- wie auch Darmbedingungen unlöslich ist, wobei das filmbildende Polymer ein Acrylharz oder Ethylcellulose ist, und ein Additiv zum Kontrollieren der Hydratationsgeschwindigkeit und Permeabilität der hydratisierbaren Diffusionsbarriere umfaßt, wobei das Additiv ausgewählt ist aus vollständig veresterten Acrylharzen, welche quaternäre Aminnebenketten, Natriumlaurylsulfat, Magnesiumstearat, Zitronensäure, Simethicon und Mischungen davon enthalten;

wobei die hydratisierbare Diffusionsbarriere im wesentlichen die Abgabe von therapeutischen Spiegeln des Arzneimittels 2-10 Stunden nach Aufnahme verzögert und anschließend eine Langzeitabgabe von therapeutischen Spiegeln des Arzneimittels liefert,

(ii) wobei die Komponente mit Langzeitabgabe einen Kern des wasserlöslichen Arzneimittels mit einem Diffusionsbarrierematerial darüber umfaßt.

Revendications

1. Préparation pharmaceutique à libération prolongée retardée, comprenant:

- (a) un noyau contenant un médicament hydro-soluble ayant une solubilité supérieure à 10 g par litre dans le fluide intestinal,
- (b) une barrière de diffusion hydratable entourant ledit noyau et ayant une épaisseur d'au moins 20 μm , ladite barrière comprenant
- un polymère filmogène qui est insoluble dans les conditions tant stomacales et intestinales, ledit polymère filmogène étant une résine acrylique ou de l'éthylcellulose, et
 - un additif pour régler la vitesse d'hydratation et la perméabilité de ladite barrière de diffusion hydratable, ledit additif étant choisi parmi les résines acryliques totalement estérifiées contenant des chaînes latérales d'amine quaternaire, le laurylsulfate de sodium, le stéarate de magnésium, l'acide citrique, la siméthicone et des mélanges de ceux-ci;
 - de sorte que la barrière de diffusion hydratable retarde substantiellement la libération de taux thérapeutiques dudit médicament dans les 2 à 10 heures après l'ingestion et fournit ensuite une libération prolongée de taux thérapeutiques dudit médicament.
2. Préparation pharmaceutique à libération prolongée retardée selon la revendication 1, dans laquelle ledit médicament hydrosoluble est choisi parmi le chlorhydrate de propranolol, le gluconate de guinidine, le chlorhydrate de diltiazem, le bromhydrate de dextrométhorphan, le chlorhydrate de diphenhydramine, le phosphate de disopyramide et le chlorhydrate de vérapamil.
 3. Préparation pharmaceutique à libération prolongée retardée selon la revendication 1, dans laquelle ledit additif, avant d'être ajouté au polymère filmogène et d'être appliqué sur ledit médicament de noyau, comprend de 3 à 50% d'une suspension de résine acrylique totalement estérifiée contenant des chaînes latérales d'amine quaternaire, de 0 à 1% de laurylsulfate de sodium, de 10 à 20% de stéarate de magnésium et de 40 à 87% d'eau.
 4. Préparation pharmaceutique à libération prolongée retardée selon la revendication 1, dans laquelle ledit additif, avant d'être ajouté au polymère filmogène et d'être appliqué sur ledit médicament de noyau, comprend de 5 à 20% de stéarate de magnésium, de 75 à 95% d'eau et de 0 à 5% d'acide citrique.
 5. Préparation pharmaceutique à libération prolongée retardée selon la revendication 1, dans laquelle ledit additif, avant d'être ajouté au polymère filmogène et d'être appliqué sur ledit médicament de noyau, comprend de 5 à 20% de stéarate de magnésium, de 80 à 95% d'eau et de 0 à 1% d'émulsion de siméthicone.
 6. Préparation pharmaceutique à libération prolongée retardée selon la revendication 1, dans laquelle ledit additif représente de 5 à 40% (sur la base des matières solides) du mélange de polymère filmogène et d'additif avant d'être appliqué sur ledit médicament de noyau.
 7. Préparation pharmaceutique à libération prolongée retardée selon la revendication 1, dans laquelle l'épaisseur de ladite barrière de diffusion hydratable est de 30 à 200 μm .
 8. Préparation pharmaceutique à libération prolongée retardée selon la revendication 7, dans laquelle ledit médicament de noyau est sous la forme de particules de 500 à 1500 μm de diamètre.
 9. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit constituant à libération prolongée retardée est sous la forme d'unités multiples de microparticules et ledit constituant à libération prolongée est sous la forme dudit médicament hydro-soluble appliqué concentriquement sur lesdites microparticules, après quoi une barrière de diffusion est appliquée sur celles-ci.
 10. Préparation pharmaceutique comprenant un mélange d'un constituant à libération prolongée retardée et d'un constituant à libération immédiate:
 - (i) ledit constituant à libération prolongée retardée comprenant
 - (a) un noyau contenant un médicament hydrosoluble ayant une solubilité supérieure à 10 g par litre dans le fluide intestinal,
 - (b) une barrière de diffusion hydratable entourant ledit noyau et ayant une épaisseur d'au moins 20 μm , ladite barrière comprenant
 - un polymère filmogène qui est insoluble dans les conditions tant stomacales et intestinales, ledit polymère filmogène étant une résine acrylique ou de l'éthylcellulose, et
 - un additif pour régler la vitesse d'hydratation et la perméabilité de ladite barrière de diffusion hydratable, ledit additif étant choisi parmi les résines acryliques totalement estérifiées

contenant des chaînes latérales d'amine quaternaire, le laurylsulfate de sodium, le stéarate de magnésium, l'acide citrique, la siméthicone et des mélanges de ceux-ci;

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de sorte que ladite barrière de diffusion hydratable retarde substantiellement la libération de taux thérapeutiques dudit médicament dans les 2 à 10 heures après l'ingestion et fournit ensuite une libération prolongée de taux thérapeutiques dudit médicament,

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(ii) ledit constituant à libération immédiate comprenant un médicament libre qui est immédiatement libéré dans l'estomac après l'ingestion.

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11. Préparation pharmaceutique selon la revendication 10, dans laquelle ledit constituant à libération prolongée retardée est sous la forme d'unités multiples de microparticules.

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12. Préparation pharmaceutique comprenant un mélange d'un constituant à libération prolongée retardée et d'un constituant à libération prolongée:

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(i) ledit constituant à libération prolongée retardée comprenant

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(a) un noyau contenant un médicament hydrosoluble ayant une solubilité supérieure à 10 g par litre dans le fluide intestinal,

(b) une barrière de diffusion hydratable entourant ledit noyau et ayant une épaisseur d'au moins 20 μm , ladite barrière comprenant

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un polymère filmogène qui est insoluble dans les conditions tant stomacales et intestinales, ledit polymère filmogène étant une résine acrylique ou de l'éthylcellulose, et

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un additif pour régler la vitesse d'hydratation et la perméabilité de ladite barrière de diffusion hydratable, ledit additif étant choisi parmi les résines acryliques totalement estérifiées contenant des chaînes latérales d'amine quaternaire, le laurylsulfate de sodium, le stéarate de magnésium, l'acide citrique, la siméthicone et des mélanges de ceux-ci;

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de sorte que ladite barrière de diffusion hydratable retarde substantiellement la libération de taux thérapeutiques dudit médicament dans

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les 2 à 10 heures après l'ingestion et fournit ensuite une libération prolongée de taux thérapeutiques dudit médicament,

(ii) ledit constituant à libération prolongée comprenant un noyau dudit médicament hydrosoluble avec une matière de barrière de diffusion sur celui-ci.